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Review Article

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Possible Triggering Effect of COVID - 19 Vaccination in Psoriasis Patients -An Essential Review

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Abstract

Psoriasis is an inflammatory skin condition characterized by a chronic relapsing course that is able to impact negatively a patient's quality of life. Diverse triggering factors can lead to psoriasis exacerbation, including vaccination, as the most common vaccine associated with psoriasis exacerbation is the vaccine against influenza. Psoriasis exacerbation has also been reported after the Pfizer and Corona Vac vaccine. Nowadays, the world scientific community agrees that vaccine is the most promising weapon against the COVID-19 infection and severity. Despite the fact that 272 vaccines against SARS-CoV-2 virus are in progress, only four of these, have been approved and subsequently distributed worldwide for use, are based on innovative procedures and are quite different from each other in terms of composition. Clinical professionals, such as dermatologists may be unfamiliar with the effects of those vaccines, however, there is the strong need for them to understand the critical role of vaccines, with a focus on the necessity to vaccinate individuals suffering from immune-mediated skin diseases, such as psoriasis. Psoriasis patients have shown morphologic alterations from chronic plaque-type to guttate psoriasis after their vaccination, however, the exact mechanism of psoriasis exacerbation remains unclear. It is possible that Th17 cells induced by COVID-19 vaccines may play a critical role. In the current pandemic situation, psoriasis patients who do not have contraindications to vaccination should benefit from COVID-19 vaccines in the prevention of severe COVID-19 infection and fatality.

The present review presents the possible implication of COVID-19 vaccination in psoriasis patients.

Keywords: COVID 19; Dermatology; Exacerbations; Psoriasis; Vaccine

Abbreviations: ACE: Angiotensin-Converting Enzyme, BCG: Bacillus Calmette-Guerin, Th: T-Helper, G-CSF: Granulocyte-Colony Stimulating Factor, MCP-1: Monocyte Chemoattractant Protein 1, MIP-1a: Macrophage Inflammatory Protein 1 Alpha, IP-10: Interferon-Inducible Protein 10, TNF: Tumor Necrosis Factor, GPP: Generalized Pustular Psoriasis, PP: Pustular Psoriasis

Introduction

Psoriasis is a chronic, immunologically mediated, cutaneous inflammatory disease affecting 1-3% of the population worldwide **[1]**, or its prevalence varies among populations and ranges from 0.5 to 11.4 % in adults **[2]**. It appears to be more prevalent among females than among males **[3].**

The disease results from the interaction between genetics and environmental factors such as stress, infections, drugs, physical trauma, and vaccination **[1,4]** causing a T-cell-mediated response **[1,5]**. The disease is also linked to immunologic factors with an increased risk of infections because of the disease itself or the use of immunosuppressive drugs **[6]**. Psoriasis is presented with well-defined, erythematous, indurated scaly plaques in the extensor surfaces, whereas scalp and nails may also be implicated. Diverse types of psoriasis have been described such as plaque-type, guttate, pustular, erythrodermic, inverse, nail, and psoriatic arthritis. As an autoimmune disease is mediated by T lymphocytes and is typically a persistent inflammatory condition with a varying lesions course of exacerbation and remission. The disease may be impaired by infection, emotional stress, genetics, local trauma, and environmental factors **[4]**. Coronavirus disease 2019, caused by the novel coronavirus SARS-CoV-2, has spread worldwide, and raised a number of concerns among patients with auto-immune diseases such as psoriasis. SARS-CoV-2 vaccination has become one of the most important factor to prevent the infection and control the pandemic. Individuals with immune-mediated inflammatory diseases were shown to be at increased risk of COVID-19-related death compared with the general population **[7]**. However, it is unknown if patients with psoriasis have higher risk of SARS-CoV-2 infection and the potential protective action of target therapy against the most severe COVID-19 clinical manifestations **[8]**. Patients with psoriasis displayed higher risk of respiratory comorbidities due to both systemic inflammation, high rate of smoking and anti-psoriatic regimens (i.e., conventional and target therapies) **[9]**.

Based on previous research in other infections and data collected during the COVID-19 pandemic **[10]** there has been concern over the harmful effect of systemic immune-suppressants, that are used for treatment of moderate to severe immune-mediated inflammatory diseases, on COVID-19 clinical outcomes. Vaccination at the present time is a critical strategy for those patients. Researches based on the general population indicated that two doses of a COVID-19 vaccine provides protection against SARS-CoV-2 infections and related adverse outcomes **[11]**. However, immunogenicity and clinical effectiveness in patients with immune-mediated inflammatory diseases who are receiving immune-suppressants remains uncertain.

COVID-19 outbreak had drastically modified the treatment of chronic inflammatory diseases such as psoriasis regarding their regular follow-up, mainly. Moreover, during lockdown several patients modified or even discontinued their anti-psoriatic treatments decreasing the overall daily functionality and quality of life **[12]**. Similarly, the National Psoriasis Foundation supports that vaccines may play a critical role in protecting psoriatic patients against SARS-CoV-2 infection and there is no need to discontinue their prescribed anti-psoriatic therapies **[13]**. As patients on immunosuppressive therapy were excluded from vaccine clinical trials, there is no data on the efficacy and safety of the novel vaccines in this patient population. While uncommon, a potential association has previously been documented between new onset or exacerbation of psoriasis in response to vaccination against Bacillus Calmette-Guerin (BCG), influenza, tetanus-diphtheria, and pneumococcal polysaccharide **[1,14-16]**. Moreover, although vaccination is a rare triggering factor for the exacerbations of several skin diseases, a potential association between vaccination and the onset or exacerbation of psoriasis has been previously demonstrated **[1,4]**. Patients may present a widespread severe psoriasis or new-onset guttate psoriasis as recent reports have linked COVID-19 vaccinations with psoriasis exacerbation **[1,17-23]**. The exact etiological relation between those conditions is not known. However, in the case of influenza vaccine-induced psoriasis, T-helper (Th)1 and 17 immunologic responses are thought to be the possible underlying mechanism **[24]**.

Although psoriasis is not a contraindication for many infectious diseases vaccinations the vaccination rate in psoriasis patients remains low because of the concerns about the safety of vaccines and unawareness of the risk of infection

[18,25].

The risk of COVID-19 disease in patients suffering from psoriasis

Few reports have investigated the risk of COVID-19 in patients with psoriasis. An association **[26]** between psoriasis and COVID-19 due to the role of angiotensin-converting enzyme (ACE) has been observed. The SARS-CoV-2 spike protein shows a strong binding affinity to the ACE2 receptor, that is expressed widely in the lungs, kidney, heart, intestine and endothelium. Moreover, basal epidermal layer and sebaceous gland cells in normal skin also characterized by ACE2 immuno-reactivity **[26]**, observation that could lead to the suggestion that skin may be a possible specific target for the SARS-CoV-2, as various cutaneous manifestations have been recorded during the course of COVID-19 pandemic. SARS-CoV-2 has also been isolated from skin samples **[27]**. Individuals with psoriasis have increased ACE serum levels and tissue ACE activity, especially in cases with erythrodermic psoriasis **[28]**, whereas ACE inhibitors are associated with the induction or deterioration of psoriasis caused by an allergic immune dependent reaction or a pharmacologic dose-dependent response **[26]**.SARS-CoV-2 targets the ACE2 receptor and the binding of coronavirus spike protein to the ACE2 receptor would result in ACE2 downregulation, process that would lead to excessive production of angiotensin by the ACE enzyme, the opposing physiological homolog of ACE2 **[29]**.

ACE overactivity in COVID-19 patients may deteriorate the psoriatic condition and promote a higher incidence of cardiovascular events in the subset of COVID-19 patients with psoriasis, finding that could affect severe psoriasis patients, as both higher ACE activity and cardiovascular comorbidities are associated with disease severity **[30]**.

Psoriasis patients may be at an increased risk of both deterioration in their condition and a higher rate of cardiovascular events in case of COVID-19 infection **[26]**. Another report investigated the association between psoriasis and COVID-19 infection and an epidemiological analysis compared gene expression across nine different inflammatory skin conditions, including psoriasis, and SARS-CoV2-infected bronchial epithelial cell lines. A genome-wide association study trans-disease meta-analysis between COVID-19 susceptibility and two skin diseases, atopic dermatitis and psoriasis was investigated, and the results confirmed that an inflammatory skin disease or skin condition increased the risk of being infected with SARS-CoV-2 **[31]**. Similarly, Diotallevi et al. **[32]** reported that patients with psoriasis are more susceptible to SARS-CoV2 infection.

COVID-19 disease as a causative factor for exacerbation of psoriasis

The increasing spread of SARS-CoV-2 infection worldwide could result in diverse consequences in individuals with skin diseases, such as psoriasis, as several researches have shown exacerbation of the disease in patients with COVID-19 **[33-40]**.

A case of a patient with psoriasis and COVID-19, treated with hydroxychloroquine and oseltamivir, who developed psoriasis exacerbation on the fourth day of treatment was recorded **[33]**.

Another report also suggested that the psoriasis exacerbation was caused by the use of hydroxychloroquine which promoted IL-17 production through p38-dependent IL-23 release, resulting in keratinocyte growth and differentiation, leading to the possibility that COVID-19 disease might trigger psoriasis exacerbation **[34]**. The researchers also showed that the COVID-19 virus may have induced an exacerbation of the disease through the production of inflammation related cytokines, such as IL-2, -7 and -10, granulocyte-colony stimulating factor (G-CSF), monocyte chemoattractant protein 1 (MCP-1), macrophage inflammatory protein 1 alpha (MIP-1a), interferon-inducible protein 10 (IP-10), and tumor necrosis factor (TNF)-α **[34]**, all molecules that are implicated in the development of psoriasis.

Generalized pustular psoriasis (GPP) can be triggered by viral infections, with few reports directly associated with COVID-19 infections **[38,40]**. Similar articles have recorded cases of the development and exacerbation of pustular psoriasis (PP) during COVID-19 infection **[38-40]**. In one of those a case of PP exacerbation secondary to COVID-19 was reported, in which the patient was also treated with hydroxychloroquine, although unlike the previously reported cases, the patient had

a hydroxychloroquine use history without exacerbation of psoriasis. It is possible that SARS-CoV-2 alone might have resulted in the PP exacerbation **[39]**. In a large international series of psoriasis patients and COVID-19 infection, the results showed 348 patients (93%) fully recovered from COVID-19, 77 (21%) were hospitalized, and 9 (2%) died. Patients under biological agents were associated with a lower risk of COVID-19-related hospitalization compared to those under systemic treatments **[10]**.

In conclusion, COVID-19 may deteriorate already existing psoriasis, trigger psoriasis de novo or modify the disease phenotype. Psoriasis patients should be consulted before getting vaccinated for COVID-19, and prompt clinical follow-up should be available if exacerbation appears. However, more studies are needed to identify the exact incidence and factors contributing to the deterioration.

The possible role of COVID-19 vaccines in psoriasis exacerbation

During COVID-19 pandemic the treatment of chronic inflammatory diseases have changed drastically. Problems with drugs availability and irregular consultations with several medical specialties including dermatology resulted in disease exacerbations. In addition, the pandemic triggered insecurity regarding the use of novel treatment regimens **[12]**. Influenza (H1N1), tetanus-diphtheria, BCG, pneumococcal pneumonia and yellow fever vaccination are triggering factors for new onset or exacerbation of psoriasis **[1,14-16]**, whereas the most reported vaccination-related psoriasis exacerbations have been classified as guttate and guttate/ plaque variants **[1]**.

The mechanisms responsible for exacerbation of psoriasis after vaccination are not yet understood. It may be due to the infectious components in the vaccine and the vaccine adjuvants. Tetanus-diphtheria vaccines induce IL-6 production, which promotes the production of Th-17 cells **[15]**. In murine models, the study of the cytokine profile after influenza vaccines, revealed a cellular response with enhanced Th-1and Th-17 immunity **[41]**. The influenza vaccine generates Th1 and Th17 immunologic reactions, which could represent a possible mechanism for vaccination-induced psoriasis **[1]**. The immunologic reaction to the influenza vaccination might rely on the generation of IL-6 and IL-22, that play a critical role in the development of the characteristic epidermal alterations of psoriasis **[4]**. In patients treated with IL-17 inhibitors, Th1 cells might be involved in the development of psoriasis exacerbations instead of Th 17 cells. SARS-CoV-2 vaccine, CoronaVac, showed an incidence of adverse events of 33-35% in phase 2 and 18.9% in Phase 3 **[42,43]**. Phase 1/2 clinical trials of the protein subunit SARS-CoV-2 vaccine also confirmed good tolerance and immune genicity **[44]**. Skin-related adverse events caused by SARS-CoV-2 vaccines in the trials comprised local pain, redness, induration, systemic rash, swelling, itch, etc. **[45]**. Moreover, many cutaneous side effects have been reported with different types of SARS-CoV-2 vaccines such as early-onset or delayed-type local injection reactions, maculopapular rash, erythema multiforme, pernio and urticarial **[46]**. To be more specific, the most common side effects of the AstraZeneca COVID-19 vaccine include injection site tenderness, malaise, fatigue, headache, fever, and flu-like symptoms **[47]**. However, data regarding the effect of COVID-19 vaccines on skin diseases, including psoriasis are not available.

A recent report recorded three cases of psoriasis patients on apremilast, who were vaccinated against COVID-19 with either Pfizer or AstraZeneca vaccine (two doses) and did not show any aggravate of their disease **[48]**.

McMahon et al. **[20]** observed cases of local site reactions, swelling, urticarial eruptions, erythema, morbilliform reactions, pernio, herpes simplex exacerbations, cosmetic filler reactions, herpes zoster, pityriasis rosea-like reactions, erythromelalgia and exacerbations of existing dermatologic disorders, after COVID-19 vaccination, however regarding the prevalence of psoriasis exacerbations, among 414 cutaneous reactions, occurred only in two patients, which seems to be very rare. Another study reported the COVID-19 vaccination of three healthcare workers with psoriasis under biologic agents (secukinumab, ixekizumab, risankizumab) with Pfizer mRNA BNT162b2 without adverse effects **[49]**. Vaccination, in general, is an unusual factor triggering psoriasis exacerbations, however an association of vaccination with the new development or exacerbation of

chronic inflammatory skin diseases such as psoriasis has been recorded **[1,17-22,50,51]**.

A case of plaque psoriasis exacerbation five days after the second dose of BNT162b2 mRNA SARSCoV-2 vaccine has been recorded **[18]**. Similarly, two cases of plaque psoriasis exacerbation after inactivated and BNT162b2 mRNA COVID-19 vaccines were also recorded, the first one appeared one month after the second dose of the first vaccine (CoronaVac) and spread gradually, the second one initiated after the first dose of the second one (Pfizer/Biontech) and widespread extension of the plaques accelerated two weeks after the second dose of vaccine. In the mentioned cases, patients were under systemic treatment for psoriasis **[50]**. Another report showed deterioration of palmoplantar psoriasis **[21]** after second dose of BNT 162b2 COVID-19 mRNA COVID-19 vaccination, whereas a brief report presented 12 cases of psoriasis exacerbations after AZD1222 and BNT162b2 COVID-19 mRNA COVID-19 vaccination **[52]**. Lehhman et al. **[53]** revealed a new-onset guttate psoriasis after the BNT162b2 mRNA vaccine that started 10 days after the first dose and exacerbated after the second dose, Onsun et al. **[23]** reported a case of GPP developed four days after the first dose of the inactivated SARS-CoV-2 vaccine in a 72-year-old male with plaque psoriasis. Perna et al. **[54]** confirmed such a finding. Ricardo et al. reported *de novo* nail psoriasis triggered by Pfizer-BioNTech in a 76-year-old female **[55]**. Elamin et al. reported a case of 66-year-old female who developed new-onset GPP after the first dose of the AstraZeneca COVID-19 vaccine **[56]**. The authors examined the possible underlying immuno-pathological mechanisms and suggested a possible connection between IFN-I and their main cellular source, the plasmacytoid dendritic cells (pDC), as a possible explanation for the development of GPP after COVID-19 vaccine **[56]**.

In psoriasis, the role of the innate immune system, especially IFN-I and pDCs, that lead to the autoimmune T-cell cascade is well known **[57,58]**, as pDCs infiltrate the skin, where they are responsible for the early disease processes mainly through pDC-derived IFN-I production **[57]**. pDCs are characteristic DCs and key effectors in innate antiviral immunity due to their potent ability to secrete elevated levels of IFN-Is **[1]**. Those cells are able to recognize nucleicacids via their endosomally localized Toll-like receptor (TLRs), TLR-9 and TLR-7, which upon activation, lead to excessive amounts of IFN-I production, which are critical cytokines functioning in controlling viral replication by inducing gene expression **[57]**. Moreover, pDCs link the innate and adaptive immunity by their ability to regulate the function of other immune cells. Under normal circumstances, pDCs are usually present in the blood and lymphoid organs however, active pDCs recruitment is observed from the blood into peripheral locations of infection or inflammation **[57]**.

A Greek cohort consisted of 14 patients with psoriasis showed generalized papulosquamous rash post-vaccination with Pfizer mRNABNT162b2, Moderna mRNA-1273, and Astra Zeneca-AZD 1222, which are either mRNA or adenovirus-based vaccines. Those effect reported after the second dose of different vaccines with no statistical difference in the Psoriasis Area Severity Index (PASI) score amongst the different vaccine groups. However, nine patients had left the treatment of psoriasis for one year and five patients were on topical treatment **[17]**. Megna et al. **[29]** observed 11 cases of psoriasis exacerbation after COVID-19 vaccination with the mentioned vaccines within a time period of four months. Six cases (54.5%) of psoriasis exacerbations due to COVID-19 vaccine observed in patients under biologic treatment. Despite the fact that according to the literature COVID-19 vaccine does not seem to induce psoriasis exacerbation in patients under biologicagents **[49,59]** the investigators found a small percentage of individuals that experienced this exacerbation nevertheless being under biologic treatment. They also suggested that systemic treatment may reduce the risk of psoriasis exacerbations after COVID-19 vaccination by the protection against the inflammatory process, which can cause the aggravation of the disease. Consequently, patients undergoing topical treatment for psoriasis have a higher risk or are more susceptible to the activation of an inflammatory process leading to new and often extensive psoriasis lesions compared with patients treated with systemic drugs. However, several systemic treatments for skin disorders have been linked to reduced vaccine-induced protective immunity **[60]**. The mechanism that implicates SARS-CoV-2 vaccine as a triggering factor for psoriasis exacerbation could be attributed to the immune

response, cell-mediated and humoral, that vaccines induce and it has been suggested that Th17 cells might play a critical role **[61]**, whereas similar studies have hypothesized that Th1 and Th17 are involved in triggering a deterioration of psoriasis after vaccination **[4]**. Wang et al. **[62]** recorded a comparable rate and similar risk factors for the deterioration of psoriasis with a previous research that examined the change of psoriasis at the early stage of COVID-19 pandemic when no vaccine was available **[63]** indicating that the deterioration could be attributed to factors beyond the disease per se. Patients with psoriasis also suffer from mental health problems and to some extent, are associated with the deterioration of psoriasis **[64]**. Gunes et al. **[1]** suggested that the mechanisms responsible for psoriasis exacerbation after vaccination it is possible to be similar with those that concern influenza vaccines, and could be attributed to both dysregulation of immune system due to viral components and vaccine adjuvants. Moreover, mRNA vaccines, like diphtheria or BCG, may are responsible for a significant increase in IL-6 production and recruitment of Th17 cells, that are involved in pathogenesis of psoriasis **[1]**. The AstraZeneca AZD1222 COVID-19 vaccine has been demonstrated to induce neutralizing antibodies and T-cell responses against the SARS-CoV-2 spike protein. In particular, it can promote a Th1- biased response with production of TNF-α and IFN-γ by CD4+ T lymphocytes **[4]**. An increase in TNF-α and IFN-γ production by CD4+ T cells has been observed 14 days after a single dose of AstraZeneca COVID-19 vaccination **[65]**. Secretion of these cytokines following vaccination seems to be responsible for the development/exacerbation of psoriasis. Psoriasis is characterized by Th1-type CD4+ T cells producing high levels of TNF-α and interferon-γ (IFN-γ). TNF-α is a pro-inflammatory cytokine in skin lesions in psoriasis patients **[66]**, whereas IFN-γ has been recognized as one of the pathogenic cytokines that can trigger inflammatory cascades and signaling pathways of psoriasis with the potential to become a severity marker **[67]**. Therefore, it is plausible that the vaccine may induce psoriasis exacerbation in susceptible individuals **[65]**. Increased Th17 reactions have been observed in severe COVID-19 disease patients. As Th17 cells play a critical role in the psoriasis pathogenesis, it can be hypothesized that the mRNA COVID-19 vaccines induce elevation of IL-6 and Th17 cells, that can contribute to the onset or exacerbation of new psoriasis in a subset of patients **[68]**.

However, the exact pathophysiology that is involved in psoriasis exacerbation after AZD1222 and BNT162b2 COVID-19 mRNA vaccines has still to be clarified, and further epidemiological studies are required. It is considered that vaccines may trigger inflammatory or autoimmune diseases through the cellular and humoral immune mechanisms they use to produce vaccine-induced immune protection **[59]**. Although a direct pathological link between SARS-CoV-2 vaccines and psoriasis exacerbation is not identified, the lack of any other triggering factors and exacerbation of the skin lesions after the second dose of vaccines may suggest an immunological relation in those cases. mRNA COVID-19 vaccines clinical trials have shown that IL-2, IL-12, TNF-a and IFN-c levels may increase after vaccination and may result in the activation of inflammatory signaling path-ways, that can lead to the onset or exacerbation of psoriasis **[69]**.Researchers have shown that proteins produced in response to the vaccine induce IL- 6 production, which, in turn, promotes the development of Th1 and Th17 cells, which trigger the release of downstream cytokines that play a critical role in the development of the epidermal alterations found in acute GPP **[15]**. The close temporal association between vaccination and the onset of acute GPP suggests a causal role. Although a case of acute GPP has been reported in a study by Onsun et al. **[23]** after the Sinovac BioTech inactivated virus vaccine (CoronoVac), this case was the first documented case of acute GPP related to an mRNA COVID-19 vaccination. GPP, that is a clinical psoriasis variant characterized by recessive mutations of the IL-36 receptor antagonist gene (IL36RN), demonstrates a prominent systemic IFN-I signature that is associated with the abnormal upregulated IL-36 activity **[58]**. The underlying immune mechanism leads to this effect in GPP, which also applies to psoriasis vulgaris, is mediated by the direct action of IL-36 on pDCs, enhancing TLR-9 activation and production of IFN-a. Those findings reveal the IL-36/IFN-I pathway as a major factor that contributes to inflammation in psoriasis **[58]**. Clinical observations have shown a significant

role of IFN-I and pDCs in psoriasis/GPP as they found psoriasis/GPP induction in patients treated with recombinant IFN-α, and the frequently reported association of psoriasis/GPP with inflammatory diseases such as alopecia areata and lupus, in which evidence suggests an important pathogenic role for IFN-I and pDCs **[58]**. Moreover, IFN-I and pDCs play a critical role against coronaviruses. Coronaviruses, including COVID-19, have been shown to be effective stimulators of pDCs, leading to strong induction of IFN-Is **[70]**.

COVID-19 vaccines, including adenovirus vector systems, and mRNA vaccines, generate immunity to COVID-19 by producing high spike-protein levels **[71]**. Although mRNA vaccines interact with various endosomal, especially TLR-7 and cytosolic innate sensors, adenovirus vaccines interact with many pattern recognition receptors, mainly TLR-9. Despite this difference, both types of vaccines lead to IFN-I production, which at least partly occurs through the pDC mediated immune response **[71]**. In conclusion, COVID-19 vaccination, or infection can activate an IFN-I-mediated immune response that may serve as a trigger to an IFN-driven inflammatory disease such as GPP in genetically susceptible individuals **[72]**. Another report **[73]** showed how stress-induced, by vaccination, increase in leukocyte circulation to the sites of immune activation could be attributed to promote immuno-protection during vaccination but may also mediate the autoimmune diseases exacerbation. The excipients included in the vaccine that may also cause anaphylaxis is another critical issue. Polyethylene-glycol in the Pfizer COVID-19 vaccine is reported to be responsible for such a side effect **[74]**.

Huang Y-W and Tsai T-F **[75]** observed that the impairment of psoriasis was defined as 50% of deterioration of PASI scores, which is mainly based on the definition of minimal significant psoriasis effectiveness endpoint **[76]** and relapse in clinical trials after stop taking of biological agents, which is 50% of reduction of PASI improvement **[77]**. The investigators **[75]** suggested that the alteration in clinical morphology should be regarded as a disease exacerbation sign after receiving the COVID-19 vaccine. It is consistent with the definition of adverse events of clinical trials of biologic agents for psoriasis. Three patients developed guttate psoriasis despite the fact that were diagnosed with chronic plaque-type psoriasis for more than a time period of 10 years. Many guttate lesions emerged four days after vaccination in one of the chronic plaque-type psoriasis patients. The mean interval between the vaccination and disease exacerbation was 9.3 days, finding that was similar to another initial study in Greece (10.36 days) **[17]**. According to previous reports, no specific type of vaccine was associated with a significantly higher rate of psoriasis exacerbation **[14]**.

In another report psoriasis in four patients exacerbated after the first dose but not after the second. Three patients received AstraZeneca vaccine, and one received Moderna vaccine. In addition to the possible triggering effect of COVID-19 vaccines, psoriasis severity may be modified by the effect of biologic agents, such as the time of treatment course initiation, treatment duration, and the interval between COVID-19 vaccination and clinic follow-up. COVID-19 vaccination may be a triggering factor for psoriasis, as suggested by the short time intervals between vaccination and psoriasis exacerbation **[15]**. It should be kept in mind that vaccines against SARS-CoV-2 may exacerbate psoriasis and patients need to be followed-up. Further epidemiological studies based on larger cohort are required to identify the exact association between SARS-CoV-2 vaccines and psoriasis exacerbation. Moreover, further studies will be required to define the efficacy of the four main SARS-CoV-2 vaccines in patients with psoriasis

Conclusion

The findings of the current study suggest an association between COVID-19 vaccinations with the available vaccines used regardless of manufacturing technology. Patients with psoriasis are more likely to have multiple comorbidities or using immuno-suppresive drugs for treatment of psoriasis which may lead to severe COVID-19 infection. COVID-19 vaccination (or infection) can activate an IFN-I-mediated immune response that may serve as a trigger to an IFN-driven inflammatory disorder such as GPP in genetically susceptible individuals. The mechanisms responsible for psoriasis exacerbation after vaccination are yet to be understood. It is possible that similarly to influenza vaccines, it may be caused by both dysregulation of immune system due to viral

components and vaccine adjuvants. Moreover, mRNA vaccines, like BCG or diphtheria, may cause a significant increase in IL-6 production and recruitment of Th17 cells, which play an important role in pathogenesis of psoriasis.

Conflict of interest and source of funding statement

The authors declare that they have no conflict of interest

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